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☐	L7	L6 and dpk	0
☐	L6	L5 and JIK	3
☐	L5	Apo2L or (Apo adj 2L)	329
☐	L4	TRAIL and (TAO kinase)	0
☐	L3	L1 and TAO kinase	0
☐	L2	L1 and screening	4
☐	L1	TRAIL and JIK	7

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               AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.

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FILE 'BIOTECHNO' ENTERED AT 11:20:11 ON 09 AUG 2006

FILE 'BIOTECHDS' ENTERED AT 11:20:11 ON 09 AUG 2006

FILE 'ESBIOBASE' ENTERED AT 11:20:11 ON 09 AUG 2006

=> s TRAIL or APO2l or (APO 2L) and apoptosis
L1 10943 TRAIL OR APO2L OR (APO 2L) AND APOPTOSIS

=> s jik or dpk or ste20 or (jnk sapk)
L2 2130 JIK OR DPK OR STE20 OR (JNK SAPK)

=> s l1 and l2
L3 19 L1 AND L2

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DUPLICATE PREFERENCE IS 'CAPLUS, BIOTECHNO, ESBIOBASE'
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L4 12 DUPLICATE REMOVE L3 (7 DUPLICATES REMOVED)

=> d l4 bib abs 1-12

L4 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:729611 CAPLUS
DN 143:206465
TI Therapeutic and carrier molecules
IN Ferrante, Antonio; Rathjen, Deborah Ann
PA Peplin Biolipids Pty Ltd, Australia
SO PCT Int. Appl., 180 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005073164	A1	20050811	WO 2005-AU98	20050128

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2004-540604P P 20040130
OS MARPAT 143:206465
AB The present invention relates generally to compds. comprising a hydrocarbon chain portion and more particular to compds. comprising chemical derivatizations of the hydrocarbon chain which are useful therapeutic and prophylactic mols. The present invention further provides compds. where

the hydrocarbon chain portion is a carrier mol. for functional groups, moieties or agents. The present invention can include naturally including polyunsatd. fatty acids as well as synthetic, modified or derivatized polyunsatd. fatty acids. Furthermore. these polyunsatd. fatty acids can be conjugated to amino acids, peptides or proteins. The compds. of the present invention are particularly useful in the treatment and prophylaxis of a range of conditions including cancers, protein kinase c(PKC)- or NFκB-related- or -associated conditions, cardiovascular conditions, pain, inflammatory conditions, vascular or immunol. conditions such as diabetes, neurol. conditions and infection by a range of viruses or prokaryotic or eukaryotic organisms. The present invention further provides pharmaceutical compns. and methods of medical treatment.

RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:447673 CAPLUS
DN 143:20875
TI Differentially expressed gene profile for diagnosing and treating mental disorders
IN Akil, Huda; Atz, Mary; Bunney, William E., Jr.; Choudary, Prabhakara V.; Evans, Simon J.; Jones, Edward G.; Li, Jun; Lopez, Juan F.; Myers, Richard; Thompson, Robert C.; Tomita, Hiroaki; Vawter, Marquis P.; Watson, Stanley
PA The Board of Trustees of the Leland Stanford Junior University, USA
SO PCT Int. Appl., 226 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005046434	A2	20050526	WO 2004-US36784	20041105
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2005209181	A1	20050922	US 2004-982556	20041104
	AU 2004289247	A1	20050526	AU 2004-289247	20041105
	CA 2543811	AA	20050526	CA 2004-2543811	20041105
	EP 1680009	A2	20060719	EP 2004-800741	20041105
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR, IS, YU				
PRAI	US 2003-517751P	P	20031105		
	US 2004-982556	A	20041104		
	WO 2004-US36784	W	20041105		

AB The present invention provides methods for diagnosing mental disorders (e.g., psychotic disorders such as schizophrenia). The present invention uses DNA microarray anal. to demonstrate differential expression of genes in selected regions of post-mortem brains from patients diagnosed with mental disorders in comparison with normal control subjects. The invention also provides methods of identifying modulators of such mental disorders as well as methods of using these modulators to treat patients suffering from such mental disorders.

L4 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN

AN 2005:1020555 CAPLUS
DN 143:320266
TI Genes with differential expression profile between human dental pulp stem cells and mesenchymal stem cells and use for regenerating tooth germ
IN Ueda, Minoru; Yamada, Yoichi
PA Hitachi Medical Corp., Japan
SO Jpn. Kokai Tokkyo Koho, 246 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 2005253442	A2	20050922	JP 2004-111582	20040309
PRAI JP 2004-111582		20040309		

AB The present invention relates to a group of genes whose expression profile are different between human dental pulp stem cells and mesenchymal stem cells, as well as a method for regenerating tooth germ using these genes. According to the present invention, the gene expression profiles and cluster anal. between human dental pulp stem cells (hDPSCs) and mesenchymal stem cells (hMSCs) as representative populations of odontoprogenitor and osteoprogenitor cell were revealed, and a group of genes whose expression profile are different between human dental pulp stem cells and mesenchymal stem cells was identified. By utilizing the groups of the genes of the present invention together with the dental pulp stem cells and mesenchymal stem cells, hard tissue such as tooth germ, dental pulp, dentin or bone can be regenerated. The present inventors investigated the gene expression profiles and cluster anal. between human dental pulp stem cells (hDPSCs) and mesenchymal stem cells (hMSCs) as representative populations of odontoprogenitor and osteoprogenitor cells, resp. At first, the present inventors confirmed the differential expression of Alkaline phosphatase (ALP) activity, Dentin matrix protein 1 (DMP 1), Dentin phosphosialoprotein (DSPP) using by real time reverse-transcriptase polymerase chain reaction (RT-PCR) in total RNA from primary cultures. The number of genes in hDPSCs(I) that were up-regulated by 2>-fold, compared to hMSCs, was 614 (Table, IV). On the other band, the number of genes down regulated by <2-fold in hDPSCs (I) was 296 (Table III, IV).

L4 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:671727 CAPLUS
DN 143:166667
TI The curcuminoids- and anthocyanins-responsive genes in human adipocytes and their use in screenings of anti-obesity and anti-diabetes drugs
IN Ueno, Yuki; Tsuda, Takanori; Takanori, Hitoshi; Yoshikawa, Toshikazu; Osawa, Toshihiko
PA Biomarker Science Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 85 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 2005198640	A2	20050728	JP 2004-53258	20040227
PRAI JP 2003-394758	A	20031125		

AB The curcuminoids- and anthocyanins-responsive gene expression profiles in adipocytes have been revealed. The curcuminoids- and anthocyanins-responsive genes are designed to be used as the index markers in the screenings of the substances that can affect the gene expression patterns in obesity and diabetes. These substances can be the candidates of anti-obesity and anti-diabetes drugs. Therefore, the groups of curcuminoids- and anthocyanins-responsive genes are intended to be used as markers in a form of kit such as DNA chip for the screening of

anti-obesity and anti-diabetes drugs.

L4 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:1127487 CAPLUS
DN 142:72870
TI Gene expression profiles in airway epithelium and their use as signatures for diagnosing disorders of the lung
IN Brody, Jerome S.; Spira, Avrum; Shah, Nila; Palma, John F.
PA Trustees of Boston University, USA; Affymetrix, Inc.
SO PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004111197	A2	20041223	WO 2004-US18492	20040610
WO 2004111197	A3	20060720		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2003-477218P	P	20030610	
US 2003-483387P	P	20030627	
US 2003-497599P	P	20030825	

AB A minimally invasive sample procurement method for obtaining airway epithelial cell RNA that can be analyzed by expression profiling, e.g., by array-based gene expression profiling, is disclosed. These methods can be used to identify patterns of gene expression that are diagnostic of lung disorders, e.g., cancer, to identify subjects at risk for developing lung disorders and to custom design an array, e.g., a microarray, for the diagnosis or prediction of lung disorders or susceptibility to lung disorders. Arrays and informative genes are also disclosed for this purpose.

L4 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:740123 CAPLUS
DN 141:254538
TI Modulators of TRAIL-induced apoptosis identified by RNAi-based phenotypic screening and related methods and therapeutic use for modulating apoptosis in cancer therapy
IN Aza-Blanc, Pedro; Cooke, Michael P.; Deveraux, Quinn L.; Cooper, Christopher L.
PA IRM LLC, Bermuda
SO PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004075839	A2	20040910	WO 2004-US5169	20040220
WO 2004075839	A3	20050331		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2005003387 A1 20050106 US 2004-783391 20040220

PRAI US 2003-448960P P 20030221

US 2003-494527P P 20030812

AB The invention provides novel modulatory polypeptides of TRAIL -induced apoptosis isolated by RNAi-based forward genomics approach. Noticeably, several modulators including DOBI, a gene required for progression of the apoptotic signal through the intrinsic mitochondrial cell death pathway, and MIRSA, a gene that acts to limit TRAIL -induced apoptosis are identified in addition to other well-characterized genes in the apoptosis pathway. Furthermore, a role for MYC and the WNT pathway in maintaining susceptibility to TRAIL is also suggested. The invention also provides methods for screening modulators of TRAIL-induced apoptosis. The methods comprise first screening test agents for modulators of a novel modulatory polypeptide of TRAIL-induced apoptosis and then further screening the identified modulating agents for modulators of TRAIL-induced apoptosis. The invention further provides methods and pharmaceutical compns. for modulating apoptosis of cells and for treating diseases and conditions such as cancers.

L4 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN

AN 2003:795846 CAPLUS

DN 139:348639

TI Identification of modulators of TRAIL-induced apoptosis via RNAi-based phenotypic screening

AU Aza-Blanc, Pedro; Cooper, Christopher L.; Wagner, Klaus; Batalov, Serge; Deveraux, Quinn L.; Cooke, Michael P.

CS Genomics Institute of the Novartis Research Foundation, San Diego, CA, 92121, USA

SO Molecular Cell (2003), 12(3), 627-637
CODEN: MOCEFL; ISSN: 1097-2765

PB Cell Press

DT Journal

LA English

AB New opportunities in mammalian functional genomics are emerging through the combination of high throughput technol. and methods that allow manipulation of gene expression in living cells. Here we describe the application of an RNAi-based forward genomics approach toward understanding the biol. and mechanism of TRAIL-induced apoptosis. TRAIL is a TNF superfamily member that induces selective cytotoxicity of tumor cells when bound to its cognate receptors. In addition to detecting well-characterized genes in the apoptosis pathway, we uncover several modulators including DOBI, a gene required for progression of the apoptotic signal through the intrinsic mitochondrial cell death pathway, and MIRSA, a gene that acts to limit TRAIL -induced apoptosis. Moreover, our data suggest a role for MYC and the WNT pathway in maintaining susceptibility to TRAIL. Collectively, these observations offer several insights on how TRAIL mediates the selective killing of tumor cells and demonstrate the utility of large-scale RNAi screens in mammalian cells.

RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1

AN 2000:668342 CAPLUS

DN 133:333926

TI Autoamplification of apoptosis following ligation of CD95-L, TRAIL and TNF-α

AU Herr, Ingrid; Posovszky, Carsten; Di Marzio, Luisa; Cifone, Maria Grazia; Boehler, Thomas; Debatin, Klaus-Michael

CS Division of Pediatric Oncology, German Cancer Research Center, Heidelberg, Germany
SO Oncogene (2000), 19(37), 4255-4262
CODEN: ONCNES; ISSN: 0950-9232
PB Nature Publishing Group
DT Journal
LA English
AB CD95-L, TNF-α and TRAIL are death-inducing ligands (DILs) which may signal apoptosis via crosslinking of their cognate receptors. The present study shows that treatment of cells with agonistic mAB αAPO-1 (CD95), recombinant TRAIL or TNF-α leads to enhanced mRNA and protein expression of each DIL with concomitant death in target cells. Immunopptn. of CD95-L protein from supernatant as well as neutralizing antibodies suggest DIL proteins to be cooperatively acting mediators of these cytotoxic activity. Autoamplification of the death signal was blocked in cells with a defect in apoptosis signaling either due to a dysfunctional FADD mol. or to the failure to activate JNK /SAPKs. Phosphorylation and enhanced binding of cJun and ATF-2 to DIL promoters suggest JNK/SAPKs as activators of these transcription factors following death receptor triggering. In consequence, autocrine production of DILs allows the spread of death signals to sensitive target cells.
RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 12 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
DUPLICATE
AN 2000:30187502 BIOTECHNO
TI Actinomycin D induces apoptosis and inhibits growth of pancreatic cancer cells
AU Kleeff J.; Kornmann M.; Sawhney H.; Korc M.
CS M. Korc, Division of Endocrinology, Diabetes and Metabolism, University of California, Irvine, CA 92697, United States.
E-mail: mkorc@uci.edu
SO International Journal of Cancer, (2000), 89/2 (399-407), 47 reference(s)
CODEN: IJCNAW ISSN: 0020-7136
DT Journal; Article
CY United States
LA English
SL English
AB Pancreatic cancer cells are usually resistant to apoptosis induced by cytotoxic drugs, by activation of surface receptors such as Fas and TNF receptor or by serum or growth factor withdrawal. Actinomycin D (actD) is an inhibitor of RNA synthesis and acts as a potent inducer of apoptosis in several cell lines. In the present study, we investigated the effects of actD on PANC-I pancreatic cancer cells. ActD caused apoptosis in PANC-I cells in a dose-dependent manner, as determined by cell growth assays, DNA laddering and TUNEL assays. Induction of apoptosis correlated with activation of the JNK/SAPK pathway and increased expression of Bax but not Bad or p53. PANC-I cells were completely resistant to Fas antibody and TNF-α. In contrast, TRAIL decreased the growth of PANC-I cells by 22%. Low concentrations of actD (10 ng/ml) enhanced the cytotoxic effects of all 3 cytokines. EGF, FGF-2 and IGF-I did not protect PANC-I cells from actD-mediated apoptosis. ActD (10 ng/ml) also inhibited the growth of CAPAN-I and T3M4 pancreatic cancer cells but not MiaPaCa-2 cells. Our observations suggest that actD may act via JNK/SAPK and Bax to promote apoptosis in PANC-I cells and that it may inhibit the growth of other pancreatic cancer cell lines. (C) 2000 Wiley-Liss, Inc.

L4 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2000:288090 CAPLUS
DN 133:187710
TI Actinomycin d induces apoptosis and inhibits growth of pancreatic cancer

cells
AU Kleeff, Jorg; Kornmann, Marko; Sawhney, Harneet; Korc, Murray
CS Division of Endocrinology, Diabetes, and Metabolism, Departments of Medicine, Biological Chemistry and Pharmacology, University of California, Irvine, CA, 92697, USA
SO International Journal of Cancer (2000), 86(3), 399-407
CODEN: IJCNAW; ISSN: 0020-7136
PB Wiley-Liss, Inc.
DT Journal
LA English
AB Pancreatic cancer cells are usually resistant to apoptosis induced by cytotoxic drugs, by activation of surface receptors such as Fas and TNF receptor or by serum or growth factor withdrawal. Actinomycin D (actD) is an inhibitor of RNA synthesis and acts as a potent inducer of apoptosis in several cell lines. In the present study, we investigated the effects of actD on PANC-1 pancreatic cancer cells. ActD caused apoptosis in PANC-1 cells in a dose-dependent manner, as determined by cell growth assays, DNA laddering and TUNEL assays. Induction of apoptosis correlated with activation of the JNK/SAPK pathway and increased expression of Bax but not Bad or p53. PANC-1 cells were completely resistant to Fas antibody and TNF-α. In contrast, TRAIL decreased the growth of PANC-1 cells by 22%. Low concns. of actD (10 ng/mL) enhanced the cytotoxic effects of all 3 cytokines. EGF, FGF-2 and IGF-1 did not protect PANC-1 cells from actD-mediated apoptosis. ActD (10 ng/mL) also inhibited the growth of CAPAN-1 and T3M4 pancreatic cancer cells but not MiaPaCa-2 cells. Our observations suggest that actD may act via JNK/SAPK and Bax to promote apoptosis in PANC-1 cells and that it may inhibit the growth of other pancreatic cancer cell lines.
RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3
AN 1999:89898 CAPLUS
DN 130:276328
TI JNK/SAPK activity is not sufficient for anticancer therapy-induced apoptosis involving CD95-L, TRAIL and TNF-α
AU Herr, Ingrid; Wilhelm, Dagmar; Bohler, Thomas; Angel, Peter; Debatin, Klaus-Michael
CS Division of Molecular Oncology, Deutsches Krebsforschungszentrum, Heidelberg, Germany
SO International Journal of Cancer (1999), 80(3), 417-424
CODEN: IJCNAW; ISSN: 0020-7136
PB Wiley-Liss, Inc.
DT Journal
LA English
AB Stress stimuli such as γ-irradiation or the anticancer drug doxorubicin activate expression of the death-inducing ligands (DILs) CD95-L, TNF-α, and TRAIL. Apoptosis induced by γ-irradiation or doxorubicin engages a FADD- and caspase-dependent apoptosis pathway which is inhibited by dominant neg. FADD or the caspase inhibitor zVAD. ZVAD did not prevent activity of JNK/SAPKs in response to doxorubicin suggesting that JNK/SAPK activity is independent of death receptor triggering during cellular stress-induced apoptosis. In addition, JNK/SAPKs remained activated by doxorubicin in resistant cell lines in which cleavage of caspases and apoptosis was not observed These data uncouple JNK/SAPK activation and apoptosis signaling and indicate that cellular stress-induced apoptosis involves signaling via DILs which is paralleled by activation of JNK/SAPKs. Activation of these kinases may contribute e.g., to the expression of mols. involved in apoptosis but is not sufficient for induction of the apoptosis program following cellular stress.

RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 4
AN 1999:164403 CAPLUS
DN 130:350220
TI JNK/SAPK activity contributes to TRAIL
-induced apoptosis
AU Herr, Ingrid; Wilhelm, Dagmar; Meyer, Eric; Jeremias, Irmela; Angel,
Peter; Debatin, Klaus-Michael
CS Division of Molecular Oncology, Deutsches Krebsforschungszentrum,
Heidelberg, Germany
SO Cell Death and Differentiation (1999), 6(2), 130-135
CODEN: CDDIEK; ISSN: 1350-9047
PB Stockton Press
DT Journal
LA English
AB The authors report here that JNK/SAPKs are activated
by TRAIL in parallel to induction of apoptosis in human T and B
cell lines. Death signaling as well as JNK/SAPK
activation by TRAIL in these cells is FADD- and
caspase-dependent since dominant-neg. FADD or the caspase inhibitor zVAD
prevented both apoptosis and JNK/SAPK activity.
JNK/SAPK activity in response to triggering of CD95 by
an agonistic antibody (αAPO-1) was also diminished by dominant-neg.
FADD or zVAD. Correspondingly, a cell line resistant to
αAPO-1-induced death exhibited cross-resistance to TRAIL
-induced apoptosis and did not upregulate JNK/SAPK
activity in response to TRAIL or αAPO-1. Inhibition of
JNK/SAPK activity, by stably transfecting cells with a
dominant-neg. JNKK-MKK4 construct, reduced apoptosis in response to
TRAIL or αAPO-1. Therefore, activation of JNK/
SAPKs by TRAIL or αAPO-1 occurs downstream of FADD
and caspases and contributes to apoptosis in human lymphoid cell lines.
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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Logon file001 09aug06 10:13:23
          *** ANNOUNCEMENTS ***
                    ***
NEW FILES RELEASED
***EMCare (File 45)
***Trademarkscan - South Korea (File 655)
***Regulatory Affairs Journals (File 183)
***Index Chemicus (File 302)
***Inspec (File 202)

RESUMED UPDATING
***File 141, Reader's Guide Abstracts
                    ***
RELOADS COMPLETED
***File 11, PsycInfo
***File 516, D&B--Dun's Market Identifiers
***File 523, D&B European Dun's Market Identifiers
***File 531, American Business Directory
*** The 2005 reload of the CLAIMS files (Files 340, 341, 942)
is now available online.
                                ***
DATABASES REMOVED
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Chemical Structure Searching now available in Prous Science Drug
Data Report (F452), Prous Science Drugs of the Future (F453),
IMS R&D Focus (F445/955), Pharmaprojects (F128/928), Beilstein
Facts (F390), Derwent Chemistry Resource (F355) and Index Chemicus
(File 302).
                    ***
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File   1:ERIC 1966-2006/Jul
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      Set  Items  Description
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Cost is in DialUnits
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B 155, 159, 10, 203, 35, 5, 467, 73, 434, 34
       09aug06 10:14:02 User290558 Session D67.1
            $0.82    0.233 DialUnits File1
     $0.82  Estimated cost File1
     $0.16  INTERNET
     $0.98  Estimated cost this search
     $0.98  Estimated total session cost   0.233 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R) 1950-2006/Aug 08
         (c) format only 2006 Dialog
  File 159:Cancerlit 1975-2002/Oct
         (c) format only 2002 Dialog
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 *File 159: Cancerlit is no longer updating.
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        (c) 2006 The Thomson Corp
  File  34:SciSearch(R) Cited Ref Sci 1990-2006/Jul W5
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S TRAIL AND JIK
          23702  TRAIL
             40  JIK
      S1      0  TRAIL AND JIK
?

S TRAIL AND APOPTOSIS
          23702  TRAIL
         552382  APOPTOSIS
      S2  8771  TRAIL AND APOPTOSIS
?

S JIK OR DPK OR STE20 OR (JNK (N) SAPK)
             40  JIK
            281  DPK
           1333  STE20
          33553  JNK
           5806  SAPK
           3782  JNK(N)SAPK
      S3  5350  JIK OR DPK OR STE20 OR (JNK (N) SAPK)
?


Set     Items   Description
S1          0   TRAIL AND JIK
S2       8771   TRAIL AND APOPTOSIS
S3       5350   JIK OR DPK OR STE20 OR (JNK (N) SAPK)
?

S S2 AND S3
          8771  S2
          5350  S3
      S4    48  S2 AND S3
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RD S4
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S5 19 RD S4 (unique items)
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TYPE S5/FULL/1-19

5/9/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

15421512 PMID: 15837763
Role of intracellular glutathione in cell sensitivity to the apoptosis induced by tumor necrosis factor {alpha}-related apoptosis-inducing ligand/anticancer drug combinations.
Meurette Olivier; Lefeuvre-Orfila Luz; Rebillard Amelie; Lagadic-Gossmann Dominique; Dimanche-Boitrel Marie-Therese
Institut National de la Sante et de la Recherche Medicale U620, Detoxication et Reparation Tissulaire, Faculte de Pharmacie, Universite Rennes 1, Rennes, France.
Clinical cancer research - an official journal of the American Association for Cancer Research (United States) Apr 15 2005, 11 (8) p3075-83, ISSN 1078-0432--Print Journal Code: 9502500
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS; Toxbib
PURPOSE: We have recently shown that combination of tumor necrosis factor alpha-related apoptosis-inducing ligand (TRAIL) with anticancer drugs induced an apoptotic cell death pathway involving both caspases and mitochondria. The present work further explores the role of intracellular reduced glutathione (GSH) level in cell sensitivity to this cell death pathway. EXPERIMENTAL DESIGN: Intracellular GSH level was measured by high-performance liquid chromatography. Cell death was detected by immunofluorescence after Hoechst 33342/propidium iodide staining. Reactive oxygen species production was evaluated by flow cytometry after dihydroethidium probe labeling. Western blot analysis was done to study stress-activated protein kinase/c-jun NH(2)-terminal kinase (SAPK/JNK) phosphorylation. The Student's t test was used to determine significance of the results. Three to six experiments were done. RESULTS: GSH depletion enhanced apoptosis induced by TRAIL/cisplatin (CDDP) or TRAIL/5-fluorouracil (5-FU) combinations in both human HT29 colon carcinoma and HepG2 hepatocarcinoma cells, whereas it enhanced cytotoxicity induced only by TRAIL/CDDP in human primary hepatocytes. Our results further suggested that GSH depletion enhanced SAPK/JNK phosphorylation upon TRAIL/5-FU exposure and likely reduced the detoxification mechanisms of CDDP in HT29 cells. Resistance of Bcl-2-expressing HT29 and HepG2 cells to combined treatment was not overcome by GSH depletion, thus indicating that Bcl-2-mediated antiapoptotic effect occurs independently of intracellular GSH level. CONCLUSION: GSH depletion could be useful to increase the therapeutic efficacy of cancer treatment by TRAIL/anticancer drug combinations. Furthermore, TRAIL/5-FU combination might be a potential anticancer treatment of human tumors, being ineffective on human primary hepatocytes and thus could be of interest in clinical cancer treatment. Nevertheless, Bcl-2 expression remains an important resistance factor.
Descriptors: *Antineoplastic Agents--pharmacology--PD; *Apoptosis--drug effects--DE; *Glutathione--metabolism--ME; *Membrane Glycoproteins --pharmacology--PD; *Tumor Necrosis Factor-alpha--pharmacology--PD; Adult; Apoptosis Regulatory Proteins; Blotting, Western; Cell Line, Tumor; Cell Survival--drug effects--DE; Chromatography, High Pressure Liquid; Cisplatin

--pharmacology--PD; Drug Resistance, Neoplasm; Fluorouracil--pharmacology --PD; Glutathione--physiology--PH; HT29 Cells; Hepatocytes--cytology--CY; Hepatocytes--drug effects--DE; Humans; Intracellular Space--drug effects --DE; Intracellular Space--metabolism--ME; JNK Mitogen-Activated Protein Kinases--metabolism--ME; Phosphorylation--drug effects--DE; Proto-Oncogene Proteins c-bcl-2--metabolism--ME; Research Support, Non-U.S. Gov't; Superoxides--metabolism--ME

CAS Registry No.: 0 (Antineoplastic Agents); 0 (Apoptosis Regulatory Proteins); 0 (Membrane Glycoproteins); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (TNF-related apoptosis-inducing ligand); 0 (Tumor Necrosis Factor-alpha); 11062-77-4 (Superoxides); 15663-27-1 (Cisplatin); 51-21-8 (Fluorouracil); 70-18-8 (Glutathione)

Enzyme No.: EC 2.7.1.37 (JNK Mitogen-Activated Protein Kinases)

Record Date Created: 20050419

Record Date Completed: 20050829

5/9/2 (Item 2 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

14919557 PMID: 15177310

Echinomycin and a novel analogue induce apoptosis of HT-29 cells via the activation of MAP kinases pathway.

Park Ju Youn; Park Su Jung; Shim Kwang Yong; Lee Kyu Jae; Kim Yun-Bong; Kim Yong Hae; Kim Soo Kie

Department of Microbiology, Wonju College of Medicine, Yonsei University, Wonju 220-701, South Korea.

Pharmacological research - the official journal of the Italian Pharmacological Society (England) Aug 2004, 50 (2) p201-7, ISSN 1043-6618--Print Journal Code: 8907422

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS; Toxbib

Echinomycin, in typical DNA minor groove binder, had comparable efficacy compared to 5-FU in the phase II trail of colon cancer treatment. To improve echinomycin's drawback (hydrophobicity, toxicity), we synthesized the YK-2000 series (echinomycin analogues). Among these, YK-2000 had the best in vitro cytotoxicity on six different human solid cancer cell lines. Echinomycin and YK-2000 were enabled to induce the apoptosis on the HT-29 colorectal cancer cell line. The hypothesis that apoptosis in the HT-29 cell was triggered by echinomycin and YK-2000 were supported through DNA laddering, poly-(ADP-ribose) polymerase (PARP) cleavage, and flow cytometric analysis. In order to explore the signaling pathway of echinomycin and YK-2000, we examined the phosphorylation of extracellular signal-regulated kinase1/2 (ERK1/2), stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK), and p38 MAP kinase. However, what the mechanism of cancer cell death would be induced by echinomycin and YK-2000 is unknown. Here, we present some evidence that one of the major apoptotic signaling pathways induced by echinomycin and YK-2000 is possibly the MAP kinases pathway in HT-29 human colon cancer cells. Copyright 2004 Elsevier Ltd.

Descriptors: *Apoptosis--drug effects--DE; *Echinomycin --analogs and derivatives--AA; *Echinomycin--pharmacology--PD; *HT29 Cells; *MAP Kinase Signaling System--physiology--PH; *Mitogen-Activated Protein Kinase Kinases --physiology--PH; Antineoplastic Agents--chemistry--CH; Antineoplastic Agents--pharmacology--PD; Cytological Techniques; DNA Fragmentation--drug

effects--DE; Echinomycin--chemistry--CH; Forecasting; Formazans; Humans; Korea; MAP Kinase Signaling System--drug effects--DE; Mitogen-Activated Protein Kinase Kinases--drug effects--DE; Research Support, Non-U.S. Gov't; Tetrazolium Salts
CAS Registry No.: 0 (Antineoplastic Agents); 0 (Formazans); 0 (MAP Kinase Signaling System); 0 (Tetrazolium Salts); 0 (YK2000); 23305-68-2 (MTT formazan); 512-64-1 (Echinomycin)
Enzyme No.: EC 2.7.1.- (Mitogen-Activated Protein Kinase Kinases)
Record Date Created: 20040604
Record Date Completed: 20050620

5/9/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14730923 PMID: 14751526
Apoptosis-modulating agents in combination with radiotherapy-current status and outlook.
Belka Claus; Jendrossek Verena; Pruschy Martin; Vink Stefan; Verheij Marcel; Budach Wilfried
Department of Radiation Oncology, Experimental Radiation Oncology, University of Tubingen, Hoppe Seyler Strasse 3, D-72076 Tubingen, Germany. belka@uni-tuebingen.de
International journal of radiation oncology, biology, physics (United States) Feb 1 2004, 58 (2) p542-54, ISSN 0360-3016--Print
Journal Code: 7603616
Publishing Model Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS; Toxbib
PURPOSE: To increase the therapeutic efficacy of ionizing radiation or to reduce radiation-mediated side effects, diverse research centers for translational radiation oncology have headed for a specific modulation of defined cellular death pathways. In this regard, several signaling systems have proved to be of high potential value. RESULTS: It has previously been shown that apoptotic pathways induced by ionizing radiation are distinct from death pathways triggered by death ligands such as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). The combination of both radiation and TRAIL was highly efficient in vitro and in preclinical mouse models. However, several aspects of normal tissue toxicity have not been solved, and no Phase I data are available yet. A second approach tested in a Phase I trial is based on the observation that synthetic phospholipid derivatives (alkyllysophospholipids and alkylphosphocholines) strongly enhance apoptotic effects by modulating the balance among the mitogenic, anti-apoptotic MAPK, phosphatidylinositol 3'-kinase (PI3K)/Akt, and the pro-apoptotic SAPK/JNK signaling pathways. Furthermore, others have provided evidence that inhibition of anti-apoptotic signals generated by mitogenic stimuli may increase radiation responses. In this context, controversial data are available regarding the influence of a pharmacologic abrogation of MEK1, Erk1/2 signaling on apoptotic sensitivity but no Phase I trials of MEK inhibitors either alone or in combination with radiation have yet been published. However, inhibition of the PI3K/Akt survival pathway using compounds such as the protein kinase C (PKC) inhibitor PKC412 has been shown to induce apoptosis or to increase the apoptotic sensitivity of tumor cells. Therefore, these drugs may be used alone or in combination with radiation to increase tumor control; however, Phase I data are lacking. Several other drugs, including cyclooxygenase-2 inhibitors,

betulinic acid, and proteasome inhibitors, have been shown to interact with apoptotic signal transduction. Again, most of the drugs have not been tested in combination with radiation in vivo or-in the case of cyclooxygenase-2 inhibitors-exert pleiotropic effects. CONCLUSION: Although the examples do not reflect all available strategies, it is clear that several promising approaches targeting defined cell death pathways have been developed and entered into clinical trials. The use of synthetic phospholipid derivatives in a Phase I trial is an important example, proving that basic research in radiation biology finally guides the development of new treatment strategies. This, and other approaches, will hopefully increase tumor control rates and reduce side effects in the future. (118 Refs.)

Descriptors: *Apoptosis--drug effects--DE; *Apoptosis--radiation effects --RE; *Membrane Glycoproteins--physiology--PH; *Neoplasms--drug therapy--DT ; *Neoplasms--radiotherapy--RT; *Tumor Necrosis Factor-alpha--physiology --PH; Antigens, CD95--physiology--PH; Apoptosis--physiology--PH; Apoptosis Regulatory Proteins; Caspases--physiology--PH; Cell Survival--physiology --PH; Genes, p53--physiology--PH; Humans; Mitochondria--physiology--PH; Radiation Tolerance; Research Support, Non-U.S. Gov't; Signal Transduction --physiology--PH

CAS Registry No.: 0 (Antigens, CD95); 0 (Apoptosis Regulatory Proteins); 0 (Membrane Glycoproteins); 0 (TNF-related apoptosis-inducing ligand); 0 (Tumor Necrosis Factor-alpha)

Enzyme No.: EC 3.4.22.- (Caspases)

Record Date Created: 20040130

Record Date Completed: 20040308

5/9/4 (Item 4 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

14656898 PMID: 14739604

Induction of necrotic tumor cell death by TRAIL/Apo-2L.

Kemp T J; Kim J-S; Crist S A; Griffith T S

Department of Urology, Interdisciplinary Graduate Program in Immunology, University of Iowa, Iowa City, IA 52242-1089, USA.

Apoptosis - an international journal on programmed cell death (United States) Dec 2003, 8 (6) p587-99, ISSN 1360-8185--Print

Journal Code: 9712129

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

A great deal of enthusiasm is being generated for TRAIL (TNF-related apoptosis-inducing ligand)/Apo-2L as a tumor therapeutic agent because it is cytotoxic to a variety of tumor cell types but not normal cells. Moreover, it is well documented that TRAIL/Apo-2L-induced tumor cell death is a caspase-dependent apoptotic process. Through the use of a transfected cell line expressing murine TRAIL/Apo-2L and a recombinant adenovirus encoding the murine TRAIL/Apo-2L cDNA (Ad5-mTRAIL) against two murine tumor cell lines [TRAMP-C2 (prostate adenocarcinoma) and Renca (renal adenocarcinoma)], we found that mTRAIL/Apo-2L also can kill tumor cells by inducing necrosis. Specifically, we observed the default method of mTRAIL/Apo-2L-induced death in TRAMP-C2 cells was via a necrotic process, characterized by the complete lack of an annexin V(+)/PI(-) population, SAPK/JNK phosphorylation, caspase activation, Bid cleavage, or cytochrome c release. Moreover, the inclusion of zVAD-fmk, an inhibitor of caspase

activation, markedly enhanced mTRAIL/Apo-2L-mediated killing of TRAMP-C2. In contrast, apoptosis was induced in TRAMP-C2 using TNF, as measured by the criteria listed above, as was Renca by mTRAIL/Apo-2L. These results demonstrate the natural occurrence of both TRAIL/Apo-2L-induced apoptotic and necrotic signaling mechanisms within tumor cells.

Descriptors: *Apoptosis--physiology--PH; *Membrane Glycoproteins --metabolism--ME; *Tumor Necrosis Factor-alpha--metabolism--ME; Animals; Apoptosis--genetics--GE; Apoptosis Regulatory Proteins; Membrane Glycoproteins--genetics--GE; Mice; Microscopy, Electron; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, Non-P.H.S.; Transfection; Tumor Cells, Cultured; Tumor Necrosis Factor-alpha--genetics--GE

CAS Registry No.: 0 (Apoptosis Regulatory Proteins); 0 (Membrane Glycoproteins); 0 (TNF-related apoptosis-inducing ligand); 0 (Tumor Necrosis Factor-alpha)

Record Date Created: 20040123

Record Date Completed: 20040719

5/9/5 (Item 5 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

13888605 PMID: 12189181

Sensitizing effects of cadmium on TNF-alpha- and TRAIL-mediated apoptosis of NIH3T3 cells with distinct expression patterns of p53.

Kim Byung Ju; Kim Mi-Suk; Kim Ki-Bae; Kim Ki-Woo; Hong Yeon-Mi; Kim In-Ki ; Lee Han-Woong; Jung Yong-Keun

Department of Life Science, Kwangju Institute of Science and Technology, 1 Oryong-dong Puk-gu, Kwangju 500-712, Korea.

Carcinogenesis (England) Sep 2002, 23 (9) p1411-7, ISSN 0143-3334--Print Journal Code: 8008055

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS; Toxbib

Tumor necrosis factor (TNF)-alpha and TNF-related apoptosis inducing ligand (TRAIL) share a common signaling pathway. Here we show a novel potentiating effect of cadmium on TNF-alpha- or TRAIL-mediated cell death via distinct signaling. TNF-alpha or TRAIL sensitized otherwise resistant NIH3T3 embryo fibroblast cells to death, when exposed to cadmium. The potentiating effects elicited by TNF-alpha or TRAIL on cell death were NF-kappaB- and SAPK/JNK-independent and were not diminished by the expression of Bcl-2. TNF-alpha potentiated the cadmium-induced accumulation of p53 but did not affect expression levels of Bax, Mdm2 and p21(WAF/CIP). A similar pattern of p53 accumulation was also observed in Balbc/3T3 fibroblasts but not in human tumor cell lines, MCF7 and HeLa cells. The synergistic cell death evoked by TNF-alpha and cadmium was attenuated by transient expression of a dominant negative p53(Val135) mutant in NIH3T3 cells and was not observed in p53(-/-) mouse embryo fibroblasts, indicating that p53 accumulation appears to contribute to cell death. In contrast, TRAIL did not further increase the cadmium-induced accumulation of p53 despite its potentiation effects on the cadmium-induced cell death. Expression of p53(Val135) mutant did not reduce TRAIL- and cadmium-mediated cell death. Taken together, these results suggest that TNF-alpha and TRAIL potentiate the cadmium-mediated cell death via distinct p53 expression patterns.

Descriptors: *Apoptosis; *Cadmium--pharmacology--PD; *Gene Expression --drug effects--DE; *Membrane Glycoproteins--pharmacology--PD; *Tumor

Necrosis Factor-alpha--pharmacology--PD; *Tumor Suppressor Protein p53 --metabolism--ME; 3T3 Cells; Animals; Antigens, CD--biosynthesis--BI; Apoptosis Regulatory Proteins; Drug Synergism; JNK Mitogen-Activated Protein Kinases; Mice; Mitogen-Activated Protein Kinases--metabolism--ME; NF-kappa B--metabolism--ME; Proto-Oncogene Proteins c-bcl-2--metabolism--ME ; Receptors, Tumor Necrosis Factor--biosynthesis--BI; Receptors, Tumor Necrosis Factor, Type I; Research Support, Non-U.S. Gov't; Tumor Suppressor Protein p53--genetics--GE

CAS Registry No.: 0 (Antigens, CD); 0 (Apoptosis Regulatory Proteins) ; 0 (Membrane Glycoproteins); 0 (NF-kappa B); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (Receptors, Tumor Necrosis Factor); 0 (Receptors, Tumor Necrosis Factor, Type I); 0 (TNF-related apoptosis-inducing ligand) ; 0 (Tumor Necrosis Factor-alpha); 0 (Tumor Suppressor Protein p53); 7440-43-9 (Cadmium)

Enzyme No.: EC 2.7.1.37 (JNK Mitogen-Activated Protein Kinases); EC 2.7.1.37 (Mitogen-Activated Protein Kinases)

Record Date Created: 20020821

Record Date Completed: 20020918

5/9/6 (Item 6 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

13882543 PMID: 12184318

[Mechanisms of radio-induced apoptosis]

Mecanismes de l'apoptose radio-induite.

Baatout Sarah; Derradji Hanane; Petitfour Olivier; von Suchodoletz Hanna; Mergeay Max

Laboratoire de Radiobiologie, Centre d'Etude de l'Energie Nucleaire, SCK-CEN, Mol, Belgique. sbaatout@sckcen.be

Canadian journal of physiology and pharmacology (Canada) Jul 2002, 80 (7) p629-37, ISSN 0008-4212--Print Journal Code: 0372712

Publishing Model Print

Document type: Journal Article; Review ; English Abstract

Languages: FRENCH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

A general overview of the activation mechanisms of programmed cell death or apoptosis following an irradiation is given in this review. First, are summarized the main induction pathways of radiation-induced apoptosis by which extracellular (tumor necrosis factor (TNF), Fas ligand, TNF-related apoptosis-inducing ligand (TRAIL)) and intracellular (mitochondria and caspases) signals are integrated. A second part is then devoted to the importance of p53 and of its regulators (ATR, ATM, DNA-PKcs) in the process of radiation-induced apoptosis. Thereafter, signal transduction pathways and more specially the role of some protein kinases (MEKK, SAPK/JNK, p38-MAPK) is treated. At last, a chapter concerns the clinical interest of radiation-induced apoptosis and the implication of apoptosis in the treatment of certain diseases. (44 Refs.)

Descriptors: *Apoptosis--radiation effects--RE; Animals; English Abstract ; Humans; Radiotherapy; Signal Transduction--radiation effects--RE; Tumor Suppressor Protein p53--genetics--GE; Tumor Suppressor Protein p53 --radiation effects--RE

CAS Registry No.: 0 (Tumor Suppressor Protein p53)

Record Date Created: 20020816

Record Date Completed: 20020927

5/9/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12676905 PMID: 10760829
Actinomycin D induces apoptosis and inhibits growth of pancreatic cancer cells.
Kleeff J; Kornmann M; Sawhney H; Korc M
Division of Endocrinology, Diabetes, and Metabolism, Departments of Medicine, Biological Chemistry and Pharmacology, University of California, Irvine, CA 92697, USA.
International journal of cancer. Journal international du cancer (UNITED STATES) May 1 2000, 86 (3) p399-407, ISSN 0020-7136--Print
Journal Code: 0042124
Contract/Grant No.: CA40612; CA; NCI
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS
Pancreatic cancer cells are usually resistant to apoptosis induced by cytotoxic drugs, by activation of surface receptors such as Fas and TNF receptor or by serum or growth factor withdrawal. Actinomycin D (actD) is an inhibitor of RNA synthesis and acts as a potent inducer of apoptosis in several cell lines. In the present study, we investigated the effects of actD on PANC-1 pancreatic cancer cells. ActD caused apoptosis in PANC-1 cells in a dose-dependent manner, as determined by cell growth assays, DNA laddering and TUNEL assays. Induction of apoptosis correlated with activation of the JNK/SAPK pathway and increased expression of Bax but not Bad or p53. PANC-1 cells were completely resistant to Fas antibody and TNF-alpha. In contrast, TRAIL decreased the growth of PANC-1 cells by 22%. Low concentrations of actD (10 ng/ml) enhanced the cytotoxic effects of all 3 cytokines. EGF, FGF-2 and IGF-I did not protect PANC-1 cells from actD-mediated apoptosis. ActD (10 ng/ml) also inhibited the growth of CAPAN-1 and T3M4 pancreatic cancer cells but not MiaPaCa-2 cells. Our observations suggest that actD may act via JNK/SAPK and Bax to promote apoptosis in PANC-1 cells and that it may inhibit the growth of other pancreatic cancer cell lines. Copyright 2000 Wiley-Liss, Inc.
Descriptors: *Antibiotics, Antineoplastic--pharmacology--PD; *Apoptosis --drug effects--DE; *Dactinomycin--pharmacology--PD; *Pancreatic Neoplasms --drug therapy--DT; *Pancreatic Neoplasms--pathology--PA; *Proto-Oncogene Proteins c-bcl-2; Antibiotics, Antineoplastic--therapeutic use--TU; Carrier Proteins--metabolism--ME; Cell Division--drug effects--DE; Dactinomycin --therapeutic use--TU; Humans; Pancreatic Neoplasms--metabolism--ME; Proto-Oncogene Proteins--metabolism--ME; Research Support, U.S. Gov't, P.H.S.; Tumor Cells, Cultured; Tumor Suppressor Protein p53--metabolism--ME ; bcl-2-Associated X Protein; bcl-Associated Death Protein
CAS Registry No.: 0 (Antibiotics, Antineoplastic); 0 (BAD protein, human); 0 (BAX protein, human); 0 (Carrier Proteins); 0 (Proto-Oncogene Proteins); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (Tumor Suppressor Protein p53); 0 (bcl-2-Associated X Protein); 0 (bcl-Associated Death Protein); 50-76-0 (Dactinomycin)
Record Date Created: 20000502
Record Date Completed: 20000502

5/9/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12359842 PMID: 10200559
JNK/SAPK activity contributes to TRAIL-induced apoptosis.
Herr I; Wilhelm D; Meyer E; Jeremias I; Angel P; Debatin K M
Division of Molecular Oncology, Deutsches Krebsforschungszentrum, Heidelberg, Germany.
Cell death and differentiation (ENGLAND) Feb 1999, 6 (2) p130-5, ISSN 1350-9047--Print Journal Code: 9437445
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS
We report here that JNK/SAPKs are activated by TRAIL in parallel to induction of apoptosis in human T and B cell lines. Death signaling as well as JNK/SAPK activation by TRAIL in these cells is FADD- and caspase-dependent since dominant-negative FADD or the caspase inhibitor zVAD prevented both, apoptosis and JNK/SAPK activity. JNK/SAPK activity in response to triggering of CD95 by an agonistic antibody (alphaAPO-1) was also diminished by dominant-negative FADD or zVAD. Correspondingly, a cell line resistant to alphaAPO-1-induced death exhibited crossresistance to TRAIL-induced apoptosis and did not upregulate JNK/SAPK activity in response to TRAIL or alphaAPO-1. Inhibition of JNK/SAPK activity, by stably transfecting cells with a dominant-negative JNKK-MKK4 construct, reduced apoptosis in response to TRAIL or alphaAPO-1. Therefore, activation of JNK/SAPKs by TRAIL or alphaAPO-1 occurs downstream of FADD and caspases and contributes to apoptosis in human lymphoid cell lines.
Descriptors: *Apoptosis--physiology--PH; *Arabidopsis Proteins; *Ca(2+)-Calmodulin Dependent Protein Kinase--metabolism--ME; *Membrane Glycoproteins--metabolism--ME; *Mitogen-Activated Protein Kinase Kinases; *Mitogen-Activated Protein Kinases; *Tumor Necrosis Factor-alpha --metabolism--ME; Antibodies--pharmacology--PD; Antigens, CD95--immunology --IM; Apoptosis Regulatory Proteins; B-Lymphocytes--metabolism--ME; Caspases--metabolism--ME; Cell Line; Enzyme Activation; Enzyme Inhibitors --pharmacology--PD; Fatty Acid Desaturases--metabolism--ME; Humans; JNK Mitogen-Activated Protein Kinases; MAP Kinase Kinase 4; Pichia--genetics --GE; Plant Proteins--metabolism--ME; Protein Kinases--genetics--GE; Research Support, Non-U.S. Gov't; Signal Transduction--physiology--PH; T-Lymphocytes--metabolism--ME; Transfection
CAS Registry No.: 0 (Antibodies); 0 (Antigens, CD95); 0 (Apoptosis Regulatory Proteins); 0 (Arabidopsis Proteins); 0 (Enzyme Inhibitors); 0 (Membrane Glycoproteins); 0 (Plant Proteins); 0 (TNF-related apoptosis-inducing ligand); 0 (Tumor Necrosis Factor-alpha)
Enzyme No.: EC 1.14.99.- (Fad7 protein, Arabidopsis); EC 1.14.99.- (Fatty Acid Desaturases); EC 2.7.1.- (MAP Kinase Kinase 4); EC 2.7.1.- (Mitogen-Activated Protein Kinase Kinases); EC 2.7.1.123 (Ca(2+)-Calmodulin Dependent Protein Kinase); EC 2.7.1.37 (JNK Mitogen-Activated Protein Kinases); EC 2.7.1.37 (Mitogen-Activated Protein Kinases); EC 2.7.1.37 (Protein Kinases); EC 3.4.22.- (Caspases)
Record Date Created: 19990429
Record Date Completed: 19990429

5/9/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12295048 PMID: 9935184
JNK/SAPK activity is not sufficient for anticancer therapy-induced

apoptosis involving CD95-L, TRAIL and TNF-alpha.
Herr I; Wilhelm D; Bohler T; Angel P; Debatin K M
Division of Molecular Oncology, Deutsches Krebsforschungszentrum, Heidelberg, Germany.
International journal of cancer. Journal international du cancer (UNITED STATES) Jan 29 1999, 80 (3) p417-24, ISSN 0020-7136--Print
Journal Code: 0042124
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS
We report here that stress stimuli such as gamma-irradiation or the anticancer drug doxorubicin activate expression of the death-inducing ligands (DILs) CD95-L, TNF-alpha and TRAIL. Apoptosis induced by gamma-irradiation or doxorubicin engages a FADD- and caspase-dependent apoptosis pathway which is inhibited by dominant negative FADD or the caspase inhibitor zVAD. zVAD did not prevent activity of JNK/SAPKs in response to doxorubicin suggesting that JNK/SAPK activity is independent of death receptor triggering during cellular stress-induced apoptosis. In addition, JNK/SAPKs remained activated by doxorubicin in resistant cell lines in which cleavage of caspases and apoptosis was not observed. These data uncouple JNK/SAPK activation and apoptosis signaling and indicate that cellular stress-induced apoptosis involves signaling via DILs which is paralleled by activation of JNK/SAPKs. Activation of these kinases may contribute e.g., to the expression of molecules involved in apoptosis but is not sufficient for induction of the apoptosis program following cellular stress.
Descriptors: *Antigens, CD95--metabolism--ME; *Apoptosis--physiology--PH; *Arabidopsis Proteins; *Ca(2+)-Calmodulin Dependent Protein Kinase --metabolism--ME; *Membrane Glycoproteins--metabolism--ME; *Mitogen-Activated Protein Kinases; *Neoplasm Proteins--metabolism--ME; *Tumor Necrosis Factor-alpha--metabolism--ME; Antineoplastic Agents--pharmacology--PD; Apoptosis Regulatory Proteins; Caspases--metabolism--ME; Doxorubicin --pharmacology--PD; Enzyme Activation; Fatty Acid Desaturases--metabolism --ME; Humans; Jurkat Cells--drug effects--DE; Jurkat Cells--radiation effects--RE; Plant Proteins--metabolism--ME; Research Support, Non-U.S. Gov't; Tumor Cells, Cultured--drug effects--DE; Tumor Cells, Cultured --radiation effects--RE; Up-Regulation; p38 Mitogen-Activated Protein Kinases
CAS Registry No.: 0 (Antigens, CD95); 0 (Antineoplastic Agents); 0 (Apoptosis Regulatory Proteins); 0 (Arabidopsis Proteins); 0 (Membrane Glycoproteins); 0 (Neoplasm Proteins); 0 (Plant Proteins); 0 (TNF-related apoptosis-inducing ligand); 0 (Tumor Necrosis Factor-alpha) ; 23214-92-8 (Doxorubicin)
Enzyme No.: EC 1.14.99.- (Fad7 protein, Arabidopsis); EC 1.14.99.- (Fatty Acid Desaturases); EC 2.7.1.123 (Ca(2+)-Calmodulin Dependent Protein Kinase); EC 2.7.1.37 (Mitogen-Activated Protein Kinases); EC 2.7.1.37 (p38 Mitogen-Activated Protein Kinases); EC 3.4.22.- (Caspases)
Record Date Created: 19990211
Record Date Completed: 19990211

5/9/10 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014408966 BIOSIS NO.: 200300367685
The Cellular Stress Pathway and Cancer Therapy-Induced Apoptosis.

AUTHOR: Herr Ingrid (Reprint); Wilhelm Dagmar (Reprint); Kolbus Andrea (Reprint); Boehler Thomas (Reprint); Posovszky Carsten (Reprint); Angel Peter (Reprint); Debatin Klaus-Michael (Reprint)
AUTHOR ADDRESS: Division of Molecular Oncology/Pediatrics, German Cancer Research Center, Heidelberg, B-W, Germany**Germany
JOURNAL: Blood 100 (11): pAbstract No. 4201 November 16, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 44th Annual Meeting of the American Society of Hematology Philadelphia, PA, USA December 06-10, 2002; 20021206
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Multiple regulatory mechanisms modify the core apoptotic machinery consisting of death receptors, mitochondria and caspases. One regulator mechanism is the cellular stress pathway to which JNK/SAPKs and their target transcription factor cJun belong. Stable transfection of Jurkat cells with a dominant-negative mutant of the upstream kinase JNKK-MKK4 resulted in the complete prevention of JNK/SAPK activation in response to cancer therapy. Concomitantly, the onset of apoptosis as assessed by phosphatidylserine exposure, loss of mitochondrial membrane potential and upregulation of CD95-L was impaired. Induction of CD95-L in vector-transfected control cells as well as reduction of apoptosis by neutralizing CD95-L antibodies supported the important role of this death ligand in cancer therapy-induced apoptosis. Accordingly, fibroblasts from Jun minus mice exhibit a strongly delayed percentage of apoptosis together with the failure to upregulate CD95-L following cellular stress. Apoptosis sensitivity of Jun minus fibroblasts was restored by retroviral transfer of CD95-L suggesting a role of cJun in transcriptional activation of CD95-L. JNK/SAPKs are also activated by crosslinking of death receptors downstream of FADD as examplified for TRAIL and CD95. Inhibition of JNK/SAPKs in Jurkat cells stably transfected with a dominant-negative JNKK-MKK4 construct reduced apoptosis in response to ligation of TRAIL and CD95. Thus, JNK/SAPKs signal apoptosis via cJun upstream and downstream of death receptors. In consequence, we found autoactivation of CD95-L, TRAIL and TNF-alpha expression following triggering of death receptors leading to autoamplification of apoptosis. Autoamplification of the death signal was blocked in cells with a defect in apoptosis signaling either due to a dysfunctional FADD molecule or to the failure to activate JNK/SAPKs. Phosporylation and enhanced binding of cJun and ATF-2 to death ligand promoters following death receptor triggering suggest JNK/SAPKs as activators. Together, autocrine production of death ligands allows the spread of apoptosis to sensitive target cells. Involvement of cellular stress signaling in apoptosis seems not to be restricted to cancer therapy but is also important for induction of apoptosis induced by other forms of cellular stress e.g. due to by ischemia in the mouse and rat brain.

REGISTRY NUMBERS: 121800-83-7: ATF-2; 81271-93-4: CD95; 155215-87-5: JNK
DESCRIPTORS:
MAJOR CONCEPTS: Blood and Lymphatics--Transport and Circulation; Enzymology--Biochemistry and Molecular Biophysics; Molecular Genetics--Biochemistry and Molecular Biophysics; Tumor Biology
BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae--Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Retroviridae--DNA and RNA Reverse Transcribing Viruses, Viruses, Microorganisms
ORGANISMS: Jurkat cell line (Hominidae)--human T lymphoma cells; mouse

(Muridae); Retrovirus (Retroviridae)--gene vector
ORGANISMS: PARTS ETC: fibroblast
COMMON TAXONOMIC TERMS: Humans; Primates; Animals; Chordates; Mammals; Nonhuman Vertebrates; Nonhuman Mammals; Rodents; Vertebrates; DNA and RNA Reverse Transcribing Viruses; Microorganisms; Viruses
DISEASES: cancer--neoplastic disease, therapy
MESH TERMS: Neoplasms (MeSH)
CHEMICALS & BIOCHEMICALS: ATF-2--binding; CD95; CD95-L {CD95-ligand}--regulation; FADD; JNK {c-jun-N-terminal kinase}--regulation; JNKK-MKK4--mutation, upstream kinase; SAPK {stress-activated mitogen activated protein kinase}--regulation; TNF-alpha {tumor necrosis factor-alpha}--expression, regulation; TRAIL--expression, regulation; c-Jun--binding, transcription factor; death receptor; phosphatidylserine
GENE NAME: mouse CD95-L gene (Muridae)--expression, regulation
MISCELLANEOUS TERMS: cellular apoptosis mechanims; cellular stress pathway; mitochondrial membrane potential; Meeting Poster; Meeting Abstract
CONCEPT CODES:
00520 General biology - Symposia, transactions and proceedings
02506 Cytology - Animal
02508 Cytology - Human
03502 Genetics - General
03506 Genetics - Animal
03508 Genetics - Human
10064 Biochemistry studies - Proteins, peptides and amino acids
10066 Biochemistry studies - Lipids
10802 Enzymes - General and comparative studies: coenzymes
12512 Pathology - Therapy
15002 Blood - Blood and lymph studies
15004 Blood - Blood cell studies
17002 Endocrine - General
24004 Neoplasms - Pathology, clinical aspects and systemic effects
24008 Neoplasms - Therapeutic agents and therapy
31500 Genetics of bacteria and viruses
33502 Virology - General and methods
BIOSYSTEMATIC CODES:
86215 Hominidae
86375 Muridae
03305 Retroviridae

5/9/11 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013291779 BIOSIS NO.: 200100463618
TNF-Related Apoptosis Inducing Ligand (TRAIL) signaling in keratinocytes
AUTHOR: Basile John Robert (Reprint); Munger Karl (Reprint)
AUTHOR ADDRESS: Harvard Medical School, Boston, MA, USA**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 42 p273 March, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 92nd Annual Meeting of the American Association for Cancer Research New Orleans, LA, USA March 24-28, 2001; 20010324
ISSN: 0197-016X
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English
REGISTRY NUMBERS: 66-81-9: cycloheximide
DESCRIPTORS:

MAJOR CONCEPTS: Integumentary System--Chemical Coordination and Homeostasis
ORGANISMS: PARTS ETC: keratinocyte--integumentary system
CHEMICALS & BIOCHEMICALS: JNK/SAPK {c-Jun N-terminal kinase/sapk}--stimulation; NF-kappa-B {nuclear factor-kappa-B}; TNF-alpha {tumor necrosis factor-alpha}--apoptotic, cytokine; TNF-related apoptosis inducing ligand {TRAIL} {tumor-necrosis factor-related apoptosis-inducing ligand}--apoptotic, cytokine; cycloheximide--protein synthesis inhibitor
MISCELLANEOUS TERMS: JNK/SAPK pathway--stimulation; NF-kappa-B pathway {nuclear factor-kappa-B pathway}; TRAIL signaling {tumor-necrosis factor-related apoptosis-inducing ligand signaling}; apoptosis; Meeting Abstract; Meeting Abstract
CONCEPT CODES:
00520 General biology - Symposia, transactions and proceedings
02506 Cytology - Animal
10060 Biochemistry studies - General
10064 Biochemistry studies - Proteins, peptides and amino acids
17002 Endocrine - General
18504 Integumentary system - Physiology and biochemistry

5/9/12 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012324285 BIOSIS NO.: 200000042598
Amplification mechanisms for death signals within CD95-, trail- and TNF-induced apoptosis
AUTHOR: Herr Ingrid (Reprint); Posovszky Carsten (Reprint); Di Marzio Luisa ; Cifone Maria Grazia; Boehler Thomas (Reprint); Debatin Klaus-Michael (Reprint)
AUTHOR ADDRESS: Division of Pediatric Oncology, German Cancer Research Center, Heidelberg, Germany**Germany
JOURNAL: Blood 94 (10 SUPPL. 1 PART 2): p156b Nov. 15, 1999 1999
MEDIUM: print
CONFERENCE/MEETING: Forty-first Annual Meeting of the American Society of Hematology New Orleans, Louisiana, USA December 3-7, 1999; 19991203
SPONSOR: The American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English
REGISTRY NUMBERS: 81271-93-4: CD95; 104404-17-3: ceramide; 9031-54-3: sphingomyelinases
DESCRIPTORS:
MAJOR CONCEPTS: Cell Biology; Immune System--Chemical Coordination and Homeostasis
BIOSYSTEMATIC NAMES: Animalia--Animalia
ORGANISMS: animal (Animalia)
COMMON TAXONOMIC TERMS: Animals
CHEMICALS & BIOCHEMICALS: CD95; JNK-SAPK {c-Jun kinase-stress-activated protein kinases}; TNF-alpha {tumor necrosis factor-alpha}; TRAIL {tumor necrosis factor-related apoptosis-inducing ligand}; ceramide; death-inducing ligands; sphingomyelinases
MISCELLANEOUS TERMS: apoptosis; death signals--amplification; Meeting Abstract; Meeting Abstract
CONCEPT CODES:
02506 Cytology - Animal
10060 Biochemistry studies - General

10502 Biophysics - General
34502 Immunology - General and methods
00520 General biology - Symposia, transactions and proceedings
BIOSYSTEMATIC CODES:
33000 Animalia

5/9/13 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011873320 BIOSIS NO.: 199900132980
JNK/SAPK activity is not sufficient for anti-cancer therapy-induced apoptosis involving CD95-L, TRAIL and TNF-alpha
AUTHOR: Herr Ingrid (Reprint); Wilhelm Dagmar; Boehler Thomas (Reprint); Angel Peter; Debatin Klaus-Michael (Reprint)
AUTHOR ADDRESS: Div. Molecular Oncol., Deutsches Krebsforschungszentrum, Heidelberg, Germany**Germany
JOURNAL: Anticancer Research 18 (6C): p4879 Nov.-Dec., 1998 1998
MEDIUM: print
CONFERENCE/MEETING: Sixth International Conference of Anticancer Research Kallithea, Halkidiki, Greece October 21-25, 1998; 19981021
ISSN: 0250-7005
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English
REGISTRY NUMBERS: 23214-92-8: doxorubicin
DESCRIPTORS:
MAJOR CONCEPTS: Cell Biology; Pharmacology; Tumor Biology
BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGANISMS: human (Hominidae)
ORGANISMS: PARTS ETC: leukemic T cells
COMMON TAXONOMIC TERMS: Animals; Chordates; Humans; Mammals; Primates; Vertebrates
CHEMICALS & BIOCHEMICALS: death inducing ligand receptors; death inducing ligands; doxorubicin--antineoplastic-drug, pharmacodynamics; CD95-ligand; JNK/SAPK {c-Jun-N-terminal kinase/stress-activated mitogen activated protein kinase}; TNF-alpha {tumor necrosis factor-alpha}; TRAIL {tumor necrosis factor-related apoptosis-inducing ligand}
METHODS & EQUIPMENT: gamma-irradiation--experimental method
MISCELLANEOUS TERMS: apoptosis; cellular stress; Meeting Abstract; Meeting Abstract
CONCEPT CODES:
02508 Cytology - Human
10060 Biochemistry studies - General
10802 Enzymes - General and comparative studies: coenzymes
15001 Blood - General and methods
22002 Pharmacology - General
24002 Neoplasms - General
34502 Immunology - General and methods
00520 General biology - Symposia, transactions and proceedings
BIOSYSTEMATIC CODES:
86215 Hominidae

5/9/14 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

13144694 EMBASE No: 2005176400

Role of intracellular glutathione in cell sensitivity to the apoptosis induced by tumor necrosis factor alpha-related apoptosis-Inducing ligand/anticancer drug combinations

Meurette O.; Lefeuvre-Orfila L.; Rebillard A.; Lagadic-Gossmann D.; Dimanche-Boitrel M.-T.

M.-T. Dimanche-Boitrel, Inst. Natl. S. de la Rech. Med. U620, 2 Av du Pr Leon Bernard, 35043 Rennes Cedex France

AUTHOR EMAIL: marie-therese.boitrel@rennes.inserm.fr

Clinical Cancer Research (CLIN. CANCER RES.) (United States) 15 APR 2005, 11/8 (3075-3083)

CODEN: CCREF ISSN: 1078-0432

DOCUMENT TYPE: Journal ; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 49

Purpose: We have recently shown that combination of tumor necrosis factor alpha-related apoptosis-inducing ligand (TRAIL) with anticancer drugs induced an apoptotic cell death pathway involving both caspases and mitochondria. The present work further explores the role of intracellular reduced glutathione (GSH) level in cell sensitivity to this cell death pathway. Experimental Design: Intracellular GSH level was measured by high-performance liquid chromatography. Cell death was detected by immunofluorescence after Hoechst 33342/propidium iodide staining. Reactive oxygen species production was evaluated by flow cytometry after dihydroethidium probe labeling. Western blot analysis was done to study stress-activated protein kinase/c-jun NHSUB2-terminal kinase (SAPK/JNK) phosphorylation. The Student's t test was used to determine significance of the results. Three to six experiments were done. Results: GSH depletion enhanced apoptosis induced by TRAIL/cisplatin (CDDP) or TRAIL/5-fluorouracil (5-FU) combinations in both human HT29 colon carcinoma and HepG2 hepatocarcinoma cells, whereas it enhanced cytotoxicity induced only by TRAIL/CDDP in human primary hepatocytes. Our results further suggested that GSH depletion enhanced SAPK/JNK phosphorylation upon TRAIL/5-FU exposure and likely reduced the detoxification mechanisms of CDDP in HT29 cells. Resistance of Bcl-2-expressing HT29 and HepG2 cells to combined treatment was not overcome by GSH depletion, thus indicating that Bcl-2- mediated antiapoptotic effect occurs independently of intracellutar GSH level. Conclusion: GSH depletion could be useful to increase the therapeutic efficacy of cancer treatment by TRAIL/anticancer drug combinations. Furthermore, TRAIL/5-FU combination might be a potential anticancer treatment of human tumors, being ineffective on human primary hepatocytes and thus could be of interest in clinical cancer treatment. Nevertheless, Bcl-2 expression remains an important resistance factor. (c) 2005 American Association for Cancer Research.

MANUFACTURER NAMES: Merck/France; Alexis/France

DRUG DESCRIPTORS:

*glutathione--endogenous compound--ec; *tumor necrosis factor related apoptosis inducing ligand--drug combination--cb; *tumor necrosis factor related apoptosis inducing ligand--pharmacology--pd; *fluorouracil--drug combination--cb; *fluorouracil--pharmacology--pd; *cisplatin--drug combination--cb; *cisplatin--pharmacology--pd

hoe 33342; propidium iodide; reactive oxygen metabolite; hydroethidine; stress activated protein kinase; antineoplastic agent--drug combination--cb ; antineoplastic agent--pharmacology--pd

MEDICAL DESCRIPTORS:

*apoptosis

drug sensitivity; cell death; experiment; cell level; measurement; high performance liquid chromatography; immunofluorescence; staining; evaluation

; flow cytometry; chemical labeling; Western blotting; protein analysis; enzyme phosphorylation; Student t test; colon carcinoma; carcinoma cell; liver cell carcinoma; cytotoxicity; liver cell; cancer cell; antineoplastic activity; human; controlled study; human cell; article; priority journal
CAS REGISTRY NO.: 70-18-8 (glutathione); 51-21-8 (fluorouracil); 15663-27-1 , 26035-31-4, 96081-74-2 (cisplatin); 23491-52-3 (hoe 33342); 25535-16-4 (propidium iodide); 38483-26-0 (hydroethidine); 155215-87-5 (stress activated protein kinase)
SECTION HEADINGS:
016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index

5/9/15 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

11872019 EMBASE No: 2002445262
Mechanisms of radiation-induced apoptosis
MECANISMES DE L'APOPTOSE RADIO-INDUITE
Baatout S.; Derradji H.; Petitfour O.; Von Suchodoletz H.; Mergeay M.
S. Baatout, Laboratoire de Radiobiologie, Ctr. d'Etude de l'Energie Nucleaire, SCK-CEN, Boeretang 200, B-2400 Mol Belgium
AUTHOR EMAIL: sbaatout@sckcen.be
Canadian Journal of Physiology and Pharmacology (CAN. J. PHYSIOL. PHARMACOL.) (Canada) 2002, 80/7 (629-637)
CODEN: CJPPA ISSN: 0008-4212
DOCUMENT TYPE: Journal ; Conference Paper
LANGUAGE: FRENCH SUMMARY LANGUAGE: ENGLISH; FRENCH
NUMBER OF REFERENCES: 44

A general overview of the activation mechanisms of programmed cell death or apoptosis following an irradiation is given in this review. First, are summarized the main induction pathways of radiation-induced apoptosis by which extracellular (tumor necrosis factor (TNF), Fas ligand, TNF-related apoptosis-inducing ligand (TRAIL)) and intracellular (mitochondria and caspases) signals are integrated. A second part is then devoted to the importance of p53 and of its regulators (ATR, ATM, DNA-PKcs) in the process of radiation-induced apoptosis. Thereafter, signal transduction pathways and more specially the role of some protein kinases (MEKK, SAPK/JNK, p38-MAPK) is treated. At last, a chapter concerns the clinical interest of radiation-induced apoptosis and the implication of apoptosis in the treatment of certain diseases.

DRUG DESCRIPTORS:
tumor necrosis factor; FAS ligand; tumor necrosis factor related apoptosis inducing ligand; caspase; protein kinase
MEDICAL DESCRIPTORS:
*apoptosis; *irradiation
extracellular space; mitochondrion; signal transduction; conference paper; priority journal
CAS REGISTRY NO.: 186322-81-6 (caspase); 9026-43-1 (protein kinase)
SECTION HEADINGS:
014 Radiology
029 Clinical and Experimental Biochemistry

5/9/16 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

14655825 Genuine Article#: 993XW Number of References: 47

Title: A novel anti-human DR5 monoclonal antibody with tumoricidal activity induces caspase-dependent and caspase-independent cell death

Author(s): Guo YB; Chen CF; Zheng Y; Zhang JC; Tao XH; Liu SL; Zheng DX (REPRINT) ; Liu YX

Corporate Source: Chinese Acad Med Sci,Inst Basic Med Sci, Natl Lab Med Mol Biol,5 Dong Dan Tiao/Beijing 100005//Peoples R China/ (REPRINT); Chinese Acad Med Sci,Inst Basic Med Sci, Natl Lab Med Mol Biol,Beijing 100005//Peoples R China/; Peking Union Med Coll,Beijing 100005//Peoples R China/; Univ Alberta,Dept Biochem,Edmonton/AB T6G 1K7/Canada/(zhengdx@tom.com)

Journal: JOURNAL OF BIOLOGICAL CHEMISTRY, 2005, V280, N51 (DEC 23), P 41940-41952

ISSN: 0021-9258 Publication date: 20051223

Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA

Language: English Document Type: ARTICLE

Geographic Location: Peoples R China; Canada

Journal Subject Category: BIOCHEMISTRY & MOLECULAR BIOLOGY

Abstract: Like anti-Fas monoclonal antibodies, some monoclonal antibodies against tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors have tumoricidal activity too. In this article we report a novel mouse anti-human DR5 monoclonal antibody, AD5-10, that induces apoptosis of various tumor cell lines in the absence of second cross-linking in vitro and showed strong tumoricidal activity in vivo. AD5-10 does not compete with TRAIL for binding to DR5 and synergizes with TRAIL to induce apoptosis of tumor cells. AD5-10 induces both caspase-dependent and caspase-independent cell death in Jurkat cells, whereas TRAIL induces only caspase-dependent cell death. We show for the first time that DR5 can mediate caspase-independent cell death, and DR5 can mediate distinct cell signals when interacting with different extracellular proteins. Studies on AD5-10 help us to understand more on the functions of DR5 and may provide new ideas for cancer immunotherapy.

Identifiers--KeyWord Plus(R): NF-KAPPA-B; TRAIL-MEDIATED APOPTOSIS; CYTOTOXIC LIGAND TRAIL; TERMINAL KINASE; JNK/SAPK ACTIVITY; HUMAN HEPATOCYTES; RECEPTORS 1; TNF FAMILY; T-CELLS; NECROSIS

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WILSON CA, 2002, V9, P1321, CELL DEATH DIFFER
ZHANG LD, 2004, V3, P296, CANCER BIOL THER

5/9/17 (Item 2 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

13604502 Genuine Article#: 898IL Number of References: 53

Title: TRAIL-induced apoptosis in gliomas is enhanced by Akt-inhibition and is independent of JNK activation

Author(s): Puduvalli VK (REPRINT) ; Sampath D; Bruner JM; Nangia J; Xu R; Kyritsis AP
Corporate Source: Univ Texas,MD Anderson Canc Ctr, Dept Neurooncol,Box 431,1515 Holcombe Blvd/Houston//TX/77030 (REPRINT); Univ Texas,MD Anderson Canc Ctr, Dept Neurooncol,Houston//TX/77030; Univ Texas,MD Anderson Canc Ctr, Dept Expt Therapeut,Houston//TX/77030; Univ Texas,MD Anderson Canc Ctr, Dept Pathol,Houston//TX/77030; Univ Ioannina,Dept Neurol,GR-45110 Ioannina//Greece/(vpuduval@mdanderson.org)
Journal: APOPTOSIS, 2005, V10, N1 (JAN), P233-243
ISSN: 1360-8185 Publication date: 20050100
Publisher: SPRINGER, VAN GODEWIJCKSTRAAT 30, 3311 GZ DORDRECHT, NETHERLANDS
Language: English Document Type: ARTICLE
Geographic Location: USA; Greece
Journal Subject Category: BIOCHEMISTRY & MOLECULAR BIOLOGY; CELL BIOLOGY
Abstract: Patients with malignant gliomas have a poor prognosis and new treatment paradigms are needed against this disease. TRAIL/Apo2L selectively induces apoptosis in malignant cells sparing normal cells and is hence of interest as a potential therapeutic agent against gliomas. To determine the factors that modulate sensitivity to TRAIL, we examined the differences in TRAIL-activated signaling pathways in glioma cells with variable sensitivities to the agent. Apoptosis in response to TRAIL was unrelated to DR5 expression or endogenous p53 status in a panel of 8 glioma cell lines. TRAIL activated the extrinsic (cleavage of caspase-8, caspase-3 and PARP) and mitochondrial apoptotic

pathways and reduced FLIP levels. It also induced caspase-dependent JNK activation, which did not influence TRAIL-induced apoptosis. Because the pro-survival PI3K/Akt pathway is highly relevant to gliomas, we assessed whether Akt could protect against TRAIL-induced apoptosis. Pretreatment with SH-6, a novel Akt inhibitor, enhanced TRAIL-induced apoptosis, suggesting a protective role for Akt. Conversely, TRAIL induced caspase-dependent cleavage of Akt neutralizing its anti-apoptotic effects. These results demonstrate that TRAIL-induced apoptosis in gliomas involves both activation of death pathways and downregulation of survival pathways. Additional studies are warranted to determine the therapeutic potential of TRAIL against gliomas.

Descriptors--Author Keywords: Akt ; apoptosis ; death receptor ; glioma ; signal transduction ; TRAIL

Identifiers--KeyWord Plus(R): NECROSIS-FACTOR-ALPHA; AKT/PROTEIN KINASE-B; LIGAND-INDUCED APOPTOSIS; FAS-MEDIATED APOPTOSIS; N-TERMINAL KINASE; CELL-DEATH; INTRACELLULAR REGULATION; HUMAN GLIOBLASTOMA; C-FLIP; JNK/SAPK ACTIVITY

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Author(s): Herr I; Posovszky C; DiMarzio L; Cifone MG; Boehler T; Debatin KM (REPRINT)
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Journal Subject Category: ONCOLOGY; BIOCHEMISTRY & MOLECULAR BIOLOGY; CELL BIOLOGY; GENETICS & HEREDITY
Abstract: CD95-L, TNP-alpha and TRAIL are death-inducing ligands (DILs) which may signal apoptosis via crosslinking of their cognate receptors, The present study shows that treatment of cells with agonistic mAB alpha APO-1 (CD95), recombinant TRAIL or TNF-alpha leads to enhanced mRNA and protein expression of each DIL with concomitant death in target cells, Immunoprecipitation of CD95-L protein from supernatant as well as neutralizing antibodies suggest DIL proteins to be cooperatively acting mediators of these cytotoxic activity, Antoamplification of the death signal was blocked in cells with a defect in apoptosis signaling either due to a dysfunctional FADD molecule or to the failure to activate JNK/SAPKs, Phosphorylation and enhanced binding of cJun and ATF-2 to DIL promoters suggest JNK/SAPKs as activators of these transcription factors following death receptor triggering, In consequence, autocrine production of DILs allows the spread of death signals to sensitive target cells.
Descriptors--Author Keywords: FADD ; JNK/SAPKs ; ATF-2 ; cJun ; APO-1/Fas
Identifiers--KeyWord Plus(R): TUMOR-NECROSIS-FACTOR; APO-1/FAS LIGAND EXPRESSION; THERAPY-INDUCED APOPTOSIS; HUMAN T-CELLS; FAS LIGAND; SIGNAL-TRANSDUCTION; JNK/SAPK ACTIVITY; ACTIVATION; PROTEIN; STRESS
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